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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/059,579	01/28/2002	Saraswati Sukumar	JHU1630-1	7778

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EXAMINER	
SITTON, JEHANNE SOUAYA	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 01/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/059,579	SUKUMAR ET AL.	
	Examiner	Art Unit	
	Jehanne Souaya Sitton	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 October 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,9-16,20-28,34-36,40 and 41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,9-16,20-28,34-36,40 and 41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Currently, claims 1, 4 9-16, 20-28, 34-36, and 40-41 are pending in the instant application. All the amendments, arguments, and declarations have been thoroughly reviewed but are deemed insufficient to place this application in condition for allowance. Any rejections not reiterated are hereby withdrawn. The following rejections are either newly applied, as necessitated by amendment, or are reiterated. They constitute the complete set being presently applied to the instant Application. Response to Applicant's arguments follow. This action is FINAL.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. The proposed drawing correction is approved by the examiner.

Specification

4. The specification is objected to. In the proposed drawing correction, the sequence of SEQ ID NO: 69 in figure 5C does not match the sequence in the sequence listing or the table on page 75. Appropriate correction is required.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

5. Claims 28, 34-36, and 40-41 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of detecting primary breast cancer in a

subject comprising contacting a nucleic acid containing specific selected from blood, plasma, lymph, duct cells, ductal lavage fluid, nipple aspiration fluid, breast tissue, lymph nodes, bone marrow, or combinations thereof of the subject with an agent that provides a determination of the methylation state of CpG islands in the promoter of RARB2 and identifying the methylation of at least one CpG island in the promoter of RARB2, wherein hypermethylation of at least one CpG island in the promoter of RARB2 nucleic acid compared with the methylation status of CpG islands in comparable samples obtained from normal subjects is indicative of primary breast cancer in the subject, does not reasonably provide enablement for a method of diagnosing primary breast cancer wherein comparison of hypermethylation of at least one CpG island in the promoter of RARB2 in a subject compared to any sample from a normal subject is diagnostic or primary breast cancer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is undue (See In re Wands, 858 F. 2d 731, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). These factors include, but are not limited to:

Quantity of Experimentation Necessary
Amount of Direction and Guidance
Presence and Absence of Working Examples
Nature of the Invention
Level of predictability and unpredictability in the art

The claims are broadly drawn to diagnosing primary breast cancer in a subject by comparing hypermethylation of at least one CpG island in the promoter of RARB2 from a

specimen selected from blood, plasma, lymph, duct cells, ductal lavage fluid, nipple aspiration fluid, breast tissue, lymph nodes, bone marrow, or combinations thereof, to any specimen in a normal subject. The specification, however, does not enable the skilled artisan to make or use the invention commensurate in scope with the claims. Although some claims are of a more limited scope, they are still too broad such that the specification does not enable the broad scope of the claims.

The specification teaches that the RARB2 promoter was unmethylated in mortal and immortalized HMEC's but was hypermethylated in 10 of 39 primary breast tumors (see p. 57). While such teachings establish an association between hypermethylation of CpG islands of the promoter of RARB2 and primary breast tumors in patients, the specification has not established that comparison can be made to any sample from a normal subject. The claims do not require that comparison be made between a breast tissue sample in the subject and a breast tissue sample in a normal subject or a lymph sample in the subject and a lymph sample in a normal subject. The specification, however, has not established that a predictable correlation can be made between comparing different samples in a subject and control. As such, specification does not enable the full scope of the broadly claimed invention.

The claims merely require a comparison between nucleic acids between two individuals, one of which is a normal subject. (The claims do not require that the samples be the same). Such analysis yields unpredictable results. For example, Lehman et al (American Journal of Pathology, vol. 160, 2002; pp 605 – 612) teaches analysis of promoter methylation of different tissue samples in different nucleic acids. With regard to 14.3.3 sigma (see Figure 3), it is apparent that merely comparing methylation status of the promoter in two different individuals

will not establish a predictable association to diagnosis of breast cancer. For example, the 14.3.3 sigma promoter is very heavily hypermethylated in normal lymph node (it is noted that such is a sample from a healthy donor) whereas normal breast epithelial cells are significantly less methylated. The skilled artisan would not be able to establish a predictable correlation between such significant changes in methylation status and breast cancer as the analysis from lymph node was from a healthy donor. Further, diagnosis of primary breast cancer based on a difference in methylation status for *any* specimen would not be predictably correlative of disease using 14.3.3 sigma because the methylation status of the promoter is the same or similar in DCIS or hyperplasia and normal lymph (such is also true for normal blood samples, see p.608, col. 1, 2nd full para). Further, the methylation status in normal breast epithelial cells and papiloma are also very similar. In addition, Lehman specifically teaches that such data excludes the use of the detection of 14.3.3 sigma hypermethylation in lymph nodes or peripheral blood for the screening for circulation tumor cells or micrometastasis that would otherwise be promising.

Therefore, based on the lack of guidance from the specification and the unpredictability taught in the art with regard to comparison between different samples from normal and patients with tumors, the skilled artisan would be required to perform undue experimentation to practice the invention as broadly as it is claimed. The teachings of Lehman establish that while that while aberrant methylation of certain genes is indicative of breast cancer or DCIS, such a correlation cannot be predictably made when comparing different types of samples in normal and diseased patients. Trial and error analysis would be required of the skilled artisan to determine whether a correlation exists between methylation status of the promoter of RARB2 in primary breast cancer patients and normal controls when comparing different types of samples, ie: breast tissue in

patient vs lymph tissue in normal subject. The teachings of the art demonstrate that such analysis is unpredictable. Accordingly, due to the lack of guidance from the specification and the unpredictability taught in the art, such analysis would be replete with trial and error analysis, the results of which are unpredictable, and is considered undue.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 28, 34-36, and 40-41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 28, the preamble recites a method for diagnosing primary breast cancer, but the final process step recites identifying the methylation status of at least one CpG island in the promoter of RARB2. Therefore, it is unclear if the method is drawn to diagnosing primary breast cancer or to detecting methylation of CpG islands in the promoter of RARB2. Further, section b of claim 28 appears to be missing a connection or recitation as to the significance of comparison between hypermethylation in normal subjects. Section b is confusing and grammatically incorrect such that it is unclear what the significance of the statement "hypermethylated compared to the methylation state of the same region of the same nucleic acid in normal subjects" is and how such further limits the claim or relates back to the preamble.

Claim Rejections - 35 USC § 102

8. Claims 1, 4, 9-16, 20-28, 34-36, and 40-41 are rejected under 35 U.S.C. 102(a) as being anticipated by Sirchia et al (Oncogene, vol. 19, pp 1556-1563, March 16, 2000).

Sirchia et al teach a method wherein the state of methylation of CpG rich region of the RARB2 promoter was determined using methylation specific PCR (see p. 1562, primers of the instantly claimed invention) in samples of breast tumor from a subject and compared to the methylation status of RARB2 promoter in normal epithelial cells (see p. 1557). Sirchia et al specifically teach sense and antisense primers for use in the method.

Response to Amendment

9. The declaration filed on October 6, 2003 under 37 CFR 1.131 has been considered but is ineffective to overcome the Sirchia reference.

The declaration states that Saraswati Sukumar is a coinventor of the application and coauthor of the Sirchia reference. The declaration further cites Nicoletta Sacchi as an additional coinventor of the claimed invention and coauthor of the Sirchia reference. The declaration, however, has not been signed or filed by Nicoletta Sacchi. Further, 4 additional inventors are included in the inventorship of the instant application, however they have not filed or signed the declaration. Also, no statement has been made as to how such inventors did or did not contribute to the subject matter claimed. MPEP 715.04 states:

The following parties may make an affidavit or declaration under 37 CFR 1.131:
(A) All the inventors of the subject matter claimed.
(B) An affidavit or declaration by less than all named inventors of an application is accepted where it is shown that less than all named inventors of an application invented the subject matter of the claim or claims under rejection. For example, one of two joint inventors is accepted where it is shown that one of the joint inventors is the sole inventor of the claim or claims under rejection.
(C) A party qualified under 37 CFR 1.42, 1.43, or 1.47 in situation where some or all of the inventors are not available or not capable of joining in the filing of the application.
(D) The assignee or other party in interest when it is not possible to produce the affidavit or declaration of the inventor. Ex parte Foster, 1903 C.D. 213, 105 O.G. 261 (Comm'r Pat. 1903).

Affidavits or declarations to overcome a rejection of a claim or claims must be made by the inventor or inventors of the subject matter of the rejected claim(s), a party qualified under 37 CFR 1.42, 1.43, or 1.47, or the assignee or other party in interest when it is not possible to produce the affidavit or declaration of the inventor(s). Thus, where all of the named inventors of a pending application are not inventors of every claim of the application, any affidavit under 37 CFR 1.131 could be signed by only the inventor(s) of the subject matter of the rejected claims. Further, where it is shown that a joint inventor is deceased, refuses to sign, or is otherwise unavailable, the signatures of the remaining joint inventors are sufficient. However, the affidavit or declaration, even though signed by fewer than all the joint inventors, must show completion of the invention by all of the joint inventors of the subject matter of the claim(s) under rejection. In re Carlson, 79 F.2d 900, 27 USPQ 400 (CCPA 1935).

Accordingly, the submission of the declaration under 37 CFR 1.131 is insufficient to overcome the rejection under 35 USC 102(a).

Conclusion

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. No claims are allowable.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Sitton whose telephone number is (703) 308-6565. The examiner can normally be reached Monday-Thursday from 8:00 AM to 5:00 PM and on alternate Fridays.

Note: The examiner's name has changed from Jehanne Souaya to Jehanne Sitton. All future correspondence to the examiner should reflect the change in name. It is also noted that after January 12, 2004, the examiner will be located at the new USPTO campus and will be reachable at telephone number (571) 272-0752.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for this Group is (703) 872-9306.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jehanne Sitton

Jehanne (Souaya) Sitton
Primary Examiner
Art Unit 1634
12/30/03